

CLAIMS

1. A method for modulating unresponsiveness of a T cell to an antigen, comprising contacting the T cell with an agent which modulates stimulation of the T cell through a CD2 surface receptor such that modulation of unresponsiveness of the T cell occurs.

2. The method of claim 1, wherein the agent which modulates stimulation of the T cell through a CD2 surface receptor is an agent which inhibits stimulation of the T cell through a CD2 surface receptor such that unresponsiveness of the T cell to the antigen is maintained.

3. A method of claim 2, wherein the agent which inhibits T cell stimulation through a CD2 surface receptor blocks an interaction of the CD2 surface receptor with a CD2 ligand.

4. A method of claim 3, wherein the CD2 ligand is LFA-3.

5. A method of claim 3, wherein the agent which blocks an interaction of the CD2 surface receptor with a CD2 ligand is selected from the group consisting of an anti-CD2 antibody and an anti-CD2 ligand antibody.

6. A method of claim 3, wherein the agent which blocks an interaction of the CD2 surface receptor with a CD2 ligand is selected from the group consisting of a soluble form of a CD2 protein and a soluble form of a CD2 ligand protein.

7. A method of claim 2, wherein the agent which inhibits T cell activation through a CD2 surface receptor acts intracellularly to inhibit an intracellular signal triggered in the T cell through the CD2 surface receptor.

8. A method of claim 7, wherein the agent acts intracellularly to inhibit the activity of a tyrosine kinase.

9. A method of claim 8, wherein the tyrosine kinase is JAK-3.

10. A method for modulating T cell unresponsiveness to an antigen in a subject, comprising administering to the subject an agent which modulates T cell activation through a CD2 surface receptor such that modulation of T cell unresponsiveness to an antigen in the subject occurs.

11. A method of claim 10, wherein the agent which modulates T cell activation through a CD2 surface receptor is an agent which inhibits T cell activation through a CD2 surface receptor such that T cell unresponsiveness to the antigen is maintained in the subject.

12. A method of claim 11, wherein the agent which inhibits T cell stimulation through a CD2 surface receptor blocks an interaction of the CD2 surface receptor with a CD2 ligand.

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13. A method of claim 12, wherein the CD2 ligand is LFA-3.

14. A method of claim 12, wherein the agent which blocks an interaction of the CD2 surface receptor with a CD2 ligand is selected from the group consisting of an anti-CD2 antibody and an anti-CD2 ligand antibody.

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15. A method of claim 12, wherein the agent which blocks an interaction of the CD2 surface receptor with a CD2 ligand is selected from the group consisting of a soluble form of a CD2 protein and a soluble form of a CD2 ligand protein.

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16. A method of claim 11, wherein the agent which inhibits T cell stimulation through a CD2 surface receptor inhibits an intracellular signal triggered in the T cell through the CD2 surface receptor.

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17. A method of claim 13, wherein the agent acts intracellularly to inhibit the activity of a tyrosine kinase.

18. A method of claim 17, wherein the tyrosine kinase is JAK-3.

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19. A method of claim 11, further comprising administering to the subject a second agent which inhibits exposure of a T11.3 neo-epitope on the CD2 surface receptor on the T cell.

20. A method of claim 19, wherein the second agent inhibits production or function of a T cell growth factor.

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21. A method of claim 20, wherein the T cell growth factor is IL-2.

22. A method of claim 11, wherein the subject is a recipient of an allogeneic or xenogeneic cell and the antigen is on a surface of the allogeneic or xenogeneic cell.

23. A method of claim 11, wherein the subject is suffering from an autoimmune
5 disease or a disorder associated with an inappropriate or abnormal immune response.

24. A method for modulating T cell unresponsiveness to an antigen in a subject, comprising administering to the subject a first agent which modulates T cell stimulation through a CD28 or CTLA4 surface receptor and a second agent which modulates T cell
10 stimulation through a CD2 surface receptor such that modulation of T cell unresponsiveness to an antigen in the subject occurs.

25. The method of claim 24, wherein the first agent is an agent which inhibits T cell stimulation through a CD2 surface receptor and the second agent is an agent which
15 inhibits T cells stimulation through a CD28 or CTLA4 surface receptor such that unresponsiveness of the T cell to an antigen in a subject is induced and maintained.

26. A method of claim 25, wherein the first agent blocks an interaction of the CD28 or CTLA4 surface receptor with a CD28 or CTLA4 ligand.
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27. A method of claim 26, wherein the CD28 or CTLA4 ligand is selected from the group consisting of B7-1 and B7-2.

28. A method of claim 26, wherein the first agent is selected from the group
25 consisting of an anti-CD28 antibody, an anti-CTLA4 antibody, an anti-B7-1 antibody and an anti-B7-2 antibody.

29. A method of claim 26, wherein the first agent is selected from the group consisting of a soluble form of a CD28 protein, a soluble form of a CTLA4 protein, a soluble
30 form of a B7-1 protein and a soluble form of a B7-2 protein.

30. A method of claim 29, wherein the first agent is a CTLA4Ig fusion protein.

31. A method of claim 25, wherein the second agent which inhibits T cell
35 stimulation through a CD2 surface receptor blocks an interaction of the CD2 surface receptor with a CD2 ligand.

32. A method of claim 31, wherein the CD2 ligand is LFA-3.

33. A method of claim 31, wherein the second agent is selected from the group consisting of an anti-CD2 antibody and an anti-CD2 ligand antibody.

5 34. A method of claim 31, wherein the second agent is selected from the group consisting of a soluble form of a CD2 protein and a soluble form of a CD2 ligand protein.

35. A method of claim 25, wherein the second agent inhibits an intracellular signal triggered in the T cell through the CD2 surface receptor.

10 36. A method of claim 35, wherein the second agent acts intracellularly to inhibit the activity of a tyrosine kinase, JAK-3.

37. A method of claim 36, wherein the tyrosine kinase is JAK-3

15 38. A method of claim 25, further comprising administering to the subject a third agent which inhibits exposure of a T11.3 neo-epitope on the CD2 surface receptor on the T cell.

20 39. A method of claim 38, wherein the third agent inhibits production or function of a T cell growth factor.

40. A method of claim 39, wherein the T cell growth factor is IL-2.

25 41. A method of claim 25, wherein the antigen is on a surface of an allogeneic or xenogeneic cell and the subject is a recipient of the allogeneic or xenogeneic cell.

42. A method of claim 25, wherein the antigen is an autoantigen.

30 43. The method of claim 1, wherein the agent which modulates stimulation of the T cell through a CD2 surface receptor is an agent which stimulates the T cell through a CD2 surface recepto, such that responsiveness to an antigen by a T cell which is unresponsive to an antigen is restored.

35 44. A method of claim 43, wherein the agent which stimulates the T cell through a CD2 surface receptor is a CD2 ligand.

45. A method of claim 44, wherein the CD2 ligand is on a surface of a cell which expresses the antigen.

46. A method of claim 45, wherein the CD2 ligand is LFA-3.

47. A method of claim 45, wherein the CD2 ligand is expressed on a cell surface by introducing into the cell a nucleic acid molecule encoding the CD2 ligand in a form
5 suitable for expression of the CD2 ligand on the cell surface.

48. A method of claim 47, wherein the cell is a tumor cell.

49. A method of claim 43, wherein the agent which stimulates the T cell through a
10 CD2 surface receptor is at least one anti-CD2 antibody.

50. A method of claim 49, wherein the at least one anti-CD2 antibody binds to a T11.3 neo-epitope on the CD2 surface receptor.

51. A method of claim 43, further comprising contacting the T cell with a second agent which stimulates exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell.
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52. A method of claim 51, wherein the second agent is IL-2 or IL-4.
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53. A method of claim 52, wherein the T cell is contacted with IL-2 or IL-4 prior to being contacted with the first agent.

54. A method for restoring a response to an antigen by a T cell which is
25 unresponsive to the antigen, comprising contacting the T cell in the presence of the antigen with a first agent which stimulates the T cell through a CD2 surface receptor and a second agent which stimulates the T cell through a CD28 or CTLA4 surface receptor such that restoration of a response to the antigen by the T cell occurs.

55. A method of claim 54, wherein the first agent which stimulates the T cell
30 through a CD2 surface receptor is a CD2 ligand.

56. A method of claim 55, wherein the CD2 ligand is on a surface of a cell which expresses the antigen.
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57. A method of claim 56, wherein the CD2 ligand is LFA-3.

58. A method of claim 56, wherein the CD2 ligand is expressed on a cell surface by introducing into the cell a nucleic acid molecule encoding the CD2 ligand in a form suitable for expression of the CD2 ligand on the cell surface.

5 59. A method of claim 58, wherein the cell is a tumor cell.

60. A method of claim 54, wherein the first agent which stimulates the T cell through a CD2 surface receptor is at least one anti-CD2 antibody.

10 61. A method of claim 66, wherein the at least one anti-CD2 antibody binds to a T11.3 neo-epitope on the CD2 surface receptor.

62. A method of claim 54, wherein the second agent which stimulates the T cell through a CD28 or CTLA4 surface receptor is a CD28 or CTLA4 ligand.

15 63. A method of claim 62, wherein the CD28 or CTLA4 ligand is on a surface of a cell which expresses the antigen.

20 64. A method of claim 62, wherein the CD28 or CTLA4 ligand is B7-1 or B7-2.

65. A method of claim 63, wherein the CD28 or CTLA4 ligand is expressed on a cell surface by introducing into the cell a nucleic acid molecule encoding the CD28 or CTLA4 ligand in a form suitable for expression of the CD28 or CTLA4 ligand on the cell surface.

25 66. A method of claim 65, wherein the cell is a tumor cell.

67. A method of claim 54, further comprising contacting the T cell with a third agent which primes the T cell for stimulation through a CD2 surface receptor.

30 68. A method of claim 67, wherein the third agent which primes the T cell for stimulation through a CD2 surface receptor stimulates exposure of a T11.3 neo-epitope on the CD2 surface receptor on the T cell.

35 69. A method of claim 68, wherein the third agent is IL-2 or IL-4.

70. A method of claim 69, wherein the T cell is contacted with IL-2 or IL-4 prior to being contacted with the first agent.

71. A method for stimulating a T cell response to a tumor cell in a subject with a tumor, comprising modifying the tumor cell to express a CD2 ligand and a CD28 or CTLA4 ligand such that stimulation of a T cell response to a tumor cell occurs.

5 72. A method of claim 71, wherein the tumor cell is modified to express a CD2 ligand and a CD28 or CTLA4 ligand by introducing into the tumor cell at least one nucleic acid encoding the CD2 ligand and the CD28 or CTLA4 ligand in a form suitable for expression of the CD2 ligand and the CD28 or CTLA4 ligand on the tumor cell surface.

10 73. A method of claim 72, wherein the tumor cell is obtained from the subject and modified *ex vivo* to form a modified tumor cell and the method further comprises administering the modified tumor cell to the subject.

15 74. A method of claim 72, wherein a first sample of tumor cells is modified to express a CD2 ligand to form a first sample of modified tumor cells and a second sample of tumor cells is modified to express a CD28 or CTLA4 ligand to form a second sample of modified tumor cells

20 75. A method of claim 74, wherein the first and second samples of modified tumor cells are administered to the subject simultaneously.

 76. A method of claim 72, wherein the first and second samples of modified tumor cells are administered to the subject sequentially.

25 77. A method of claim 71, further comprising contacting T cells of the subject with an agent that stimulates exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell.

30 78. A method of claim 77, wherein the agent is IL-2 or IL-4.

 79. A method of claim 78, wherein T cells are obtained from the subject and contacted with IL-2 or IL-4 *ex vivo* and the method further comprises readministering the T cells to the subject.

35 80. A tumor cell which is modified to express a CD2 ligand, wherein the tumor cell does not express the CD2 ligand prior to modification.

 81. The tumor cell of claim 80, wherein the CD2 ligand is LFA-3.

82. A tumor cell which is modified to express a CD2 ligand and at least one CD28 or CTLA4 ligand, wherein the tumor cell does not express the CD2 ligand or the at least one CD28 or CTLA4 ligand prior to modification.

5 83. The tumor cell of claim 82, wherein the CD2 ligand is LFA-3 and the at least one CD28 or CTLA4 ligand is B7-1 or B7-2.

84. A method for maintaining T cell unresponsiveness to allogeneic or xenogeneic cells in a subject, comprising administering to the subject an agent which inhibits stimulation
10 of a T cell through a CD2 surface receptor such that maintenance of T cell unresponsiveness to allogeneic or xenogeneic cells occurs.

85. A method of claim 84, wherein the agent which inhibits T cell stimulation through a CD2 surface receptor blocks an interaction of the CD2 surface receptor with a CD2
15 ligand.

86. A method of claim 85, wherein the CD2 ligand is LFA-3.

87. A method of claim 85, wherein the agent which blocks an interaction of the
20 CD2 surface receptor with a CD2 ligand is selected from the group consisting of an anti-CD2 antibody and an anti-CD2 ligand antibody.

88. A method of claim 85, wherein the agent which blocks an interaction of the
25 CD2 surface receptor with a CD2 ligand is selected from the group consisting of a soluble form of a CD2 protein and a soluble form of a CD2 ligand protein.

89. A method of claim 84, wherein the agent which inhibits T cell activation through a CD2 surface receptor acts intracellularly to inhibit an intracellular signal triggered in the T cell through the CD2 surface receptor.
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90. A method of claim 84, wherein the subject is a recipient of a bone marrow transplant.

91. A method of claim 90, further comprising contacting bone marrow cells with
35 an agent which inhibits stimulation of a T cell through a CD2 surface receptor prior to transplantation into the recipient.